REMARKS

Applicant has received and reviewed an Office Action dated July 22, 2009. By way of response, Applicants have cancelled claims 87 and 121 without prejudice and amended claims 1 and 14. No new matter has been added. Claims 1-3, 10-11, 14-15, 83-86, 88-120, and 122-146 are pending.

Applicant submits that the amended claims are supported by the specification as filed. Claim 1 now includes subject matter of canceled claim 121. Claim 14 now includes subject matter of canceled claim 87.

For the reasons presented below, Applicant respectfully submits that the amended claims are in condition for allowance, and notification to that effect is earnestly solicited.

Rejection of Claims Under 35 U.S.C. §§ 102(e) and/or 103(a)

The Examiner rejected claims 1-3, 10, 11, 14, 15, 83-109, 112-142 and 146 under 35 U.S.C. § 102(e) as anticipated by Shair et al., US 2002/0090728. The Examiner rejected claims 1-3, 10, 11, 14, 15 and 83-146 under 35 U.S.C. § 103(a) over Shair in view of Heller et al., US 5,632,957. Applicant respectfully traverses these rejections.

The Shair et al. Reference Requires that the Immobilized Molecules Are *Not* in Proximity and that Two or More Immobilized Molecules Do *Not* Work Together

Before this amendment, independent claim 14 recited "2 or more of the different building block molecules together forming the candidate artificial receptor, the lead artificial receptor, the working artificial receptor, or combination thereof". That is, 2 or more building block molecules form an artificial receptor for a test ligand. This feature has been emphasized by the present amendment, which adds to each independent claim the recitation that "2 or more of the different building block molecules" are "in proximity to one another and together" form "a candidate artificial receptor, a lead artificial receptor, a working artificial receptor, or a combination thereof".

As defined in the specification as filed, the term "proximity" as applied to the present building block molecules refers to:

> "a density of building blocks sufficient to provide interactions of more than one building block with a ligand. That is, the building blocks can be in proximity to

> one another. Proximity of different building blocks can be detected by determining different (e.g., greater) binding of a test ligand to a spot or surface including a plurality of building blocks compared to a spot or surface including only one of the building blocks." (Application as filed at least at page 14, lines 10-16)

More than one building block molecule interacts with the test ligand to provide advantageous binding to the artificial receptor.

In distinct contrast, the Shair et al. reference discloses a system and method in which a molecule in a mixture reacts with an immobilized molecule independently of any other immobilized molecule. No other immobilized molecule affects this reaction with the molecule in the mixture. For the system and method described in the Shair et al. reference to work at all requires that the reactions be independent. The molecules in solution react with one immobilized molecule at a time, no other immobilized molecule affects that reaction. Thus, the immobilized molecules in the system disclosed by the Shair et al. reference are not in proximity to one another. Nor do 2 or more molecules immobilized according to the disclosure of the Shair et al. reference together form an artificial receptor.

The Shair et al. reference employs an array system for determining enantiomeric excess produced by enantioselective catalysts and reactions. Enantiomers of a single molecule are bound to a spot in an array. The enantiomers react at different rates with chiral dyes. These different reaction rates produce different colors in spots with different ratios of the enantiomers of the single molecule. Through use of standards, the ratios of the colors can be correlated with ratio of the enantiomers (the enantiomeric excess).

The system and method described in the Shair et al. reference are premised on an independent reaction of the immobilized molecule (enantiomer), and the reference proves that the reactions are independent. The Shair et al. reference presents the equations demonstrating that the molecule in solution reacts independently with the immobilized molecule at Figure 2, paragraph 60 at page 6, and paragraphs 98-100 at page 10. These equations convert the ratio of color intensities to the enantiomeric ratio. Factor "s" in these equations is defined as a ratio of rate constants. This ratio indicates that the rate constants are independent as one another. That is, the reaction of one enantiomer bound to the array does not affect the reaction of the other enantiomer. Put another way, the enantiomers do not cooperate with one another and they are not in proximity to one another. Thus, the system of the Shair et al. reference does not include

building block molecules in proximity to one another in a spot in an array. Thus, the Shair et al. reference neither teaches nor suggests the presently claimed methods.

The Shair et al. reference employs words as well as mathematics to describe these independent reactions of the immobilized molecules (enantiomer). Specifically, the Shair et al. reference states:

> "reaction between one chiral detecting agent (A) and one enantiomeric product (Al) occurs to form a diastereomeric product, while a reaction between a second chiral detecting agent (B) and a second enantiomeric product (B1) occurs to form a diastereomeric product." (paragraph 59);
>
> "because each chiral detecting agent reacts selectively (e.g., a kinetic resolution is effected) with a specific enantiomeric product via the chiral agent component, and has a detecting agent associated therewith, each enantiomeric product can be uniquely identified" (paragraph 60);
>
> "That is, chiral agent (A_r) is capable of reacting selectively (i.e., faster) with only one of the enantiomeric products, while chiral agent (A_s) is capable of reacting selectively (i.e., faster) with only the other enantiomeric product (that did not react in that manner with chiral agent A_s)." (paragraph 80);
>
> "each of said chiral detecting reagents in a set is capable of selectively reacting with one enantiomeric reaction product" (paragraph 13, and nearly identical text in paragraphs 18 and 21).

This text describes that the system of the Shair et al. reference does not include immobilized building block molecules in proximity to one another and that work together to form an artificial receptor. Thus, the Shair et al. reference neither teaches nor suggests the presently claimed methods.

The secondary references do not remedy the shortcomings of the primary reference. Thus, the combined references fail to render the presently claimed invention obvious.

The Shair et al. Reference Requires an Immobilized Molecule Known to React with the Molecule in Solution

Independent claims 1 and 25 recite, "at least one of the building block molecules being naïve with respect to a test ligand". The present application as filed defines "naïve" as:

> As used herein, the term "naïve" used with respect to one or more building blocks refers to a building block that has not previously been determined or known to bind to a test ligand of interest. For example, the recognition element(s) on a naïve building block has not previously been determined or known to bind to a test ligand of interest. A building block that is or includes a known ligand (e.g.,

> GM1) for a particular protein (test ligand) of interest (e.g., cholera toxin) is not naïve with respect to that protein (test ligand). (Specification as filed at paragraph bridging pages 10-11)

In distinct contrast, the system and method of the Shair et al. reference requires that the immobilized molecule be known to react with the molecule in solution (paragraphs 8, 10, 57-66, 98, 99, 250-252, and 268-270 and Figures 1, 2, 4-6, and 12-15). The method and system of the Shair et al. reference is inoperative unless the immobilized molecule and the molecule in solution are selected to react with one another. Employing a building block molecule that is previously not known to bind to a ligand of interest is not obvious in light of a reference that employs a pair of molecules that are known to react with one of them being immobilized before the reaction.

According to the Shair et al. reference, a reaction product or mixture is immobilized in a spot on an array where it undergoes a known interaction or reaction with a chiral detecting agent, identification moiety, or identification reagent. Specifically, the Shair et al. reference states:[1]

> "Using the principles as set forth herein, to generate a tailored set of chiral detection reagents involves: 1) selecting a desired reaction or set of reactions to

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[1] Additional statements to this effect in the Shair et al. reference include:
"each of said chiral detecting reagents in a set is capable of selectively reacting with one enantiomeric reaction product" (paragraph 13, and nearly identical text in paragraphs 18 and 21);
"the identification moiety is capable of reacting with specific functional groups in a reaction mixture" (paragraph 23);
"In general, the method of the present invention involves ... whereby interaction of the identification reagents with the components of the reaction mixtures enables determination of the identity of the reaction components" (paragraph 57);
"whereby the interaction of the chiral detecting reagents with the reaction products enables rapid analysis" (paragraph 58);
"the method of the present invention takes advantage of the principles of kinetic resolution, in which a preferential reaction occurs (at a faster rate) between one chiral reagent and one enantiomeric product" (paragraph 58);
"interaction of the identification reagents with a reaction mixture enables the determination of the identity of one or more components of a reaction mixture" (paragraph 59);
"the identifier moiety comprises a reagent that is capable of interacting selectively with a particular functional group" (paragraph 61);
"each agent in a set reacts at a different rate with each enantiomer in a reaction mixture, and thus reaction between one chiral detecting agent (A) and one enantiomeric product (A1) occurs to form a diastereomeric product, while a reaction between a second chiral detecting agent (B) and a second enantiomeric product (B1) occurs to form a diastereomeric product. Furthermore, the attachment of each one of the pair of chiral agents to a uniquely identifiable detecting agent allows rapid analysis of the reaction products by scanning methods." (paragraph 59);
"because each chiral detecting agent reacts selectively (e.g., a kinetic resolution is effected) with a specific enantiomeric product via the chiral agent component, and has a detecting agent associated therewith, each enantiomeric product can be uniquely identified" (paragraph 60).

analyze (e.g., chiral reduction of ketones to alcohols), 2) selecting a chiral reagent that is capable of reacting with the resulting functionality (alcohols) to generate a diastereomeric product that can be readily detected (via attachment to a detection agent, as described herein), and 3) testing the ability of the chiral reagent to interact selectively (react faster to effect a kinetic resolution) with one enantiomer present in a reaction mixture. That is, for a given pair of chiral reagents (enantiomeric pair), it is necessary to ensure that one in the pair will react selectively with one enantiomer present in a reaction mixture and that the second in the pair will react selectively with the other enantiomer present in a reaction mixture." (emphasis added, paragraph 66);

"As described above, the method of the present invention takes advantage of the ability of one identification reagent in a pair (or set) to react selectively (e.g., reaction occurs faster to effect a kinetic resolution, or occurs because of functional group selectivity) with one or more components of a reaction mixture over one or more of the other components. For example, a set of identification reagents can be provided to identify functional groups (and thus to potentially determine % yield or to screen new reactions), or to determine enantiomeric excess (by selective reaction with one enantiomer over another)." (paragraph 77);

"As discussed above, the method of the present invention utilizes the ability of chiral detecting agents to selectively react (i.e., react faster) with one enantiomer over another competing enantiomer. Thus, according to the method of the present invention, each enantiomeric form of a particular chiral agent present in the chiral detecting agent is capable of selectively reacting with one enantiomer of the reaction products over the other. That is, chiral agent (A_r) is capable of reacting selectively (i.e., faster) with only one of the enantiomeric products, while chiral agent (A_s) is capable of reacting selectively (i.e., faster) with only the other enantiomeric product (that did not react in that manner with chiral agent A_s). As discussed previously, selecting a particular chiral reagent for the chiral detecting reagent, the particular reaction to be analyzed must be taken into consideration to ensure that, for the set of chiral detecting reagents employed, each chiral detecting reagent within the set will contain a functionality that is capable of interacting with the reaction product, but will also react selectively with one enantiomeric product over the other. That is, in the method of the present invention, any chiral group may be utilized that is capable of effecting a kinetic resolution, as described herein, by forming a covalent bond or interaction with the substrate and producing a diastereomeric product that can be readily detected." (paragraph 80).

This text describes that the system of the Shair et al. reference requires that the immobilized molecule be known to react with the molecule in solution. The method and system of the Shair et al. reference is inoperative unless the immobilized molecule and the molecule in solution are selected to react with one another. Thus, the Shair et al. reference neither teaches nor suggests the presently claimed methods.

The secondary references do not remedy the shortcomings of the primary reference. Thus, the combined references fail to render the presently claimed invention obvious.

The Shair et al. Reference, Like Other Conventional Systems, Employs the Array as a Container

The Shair et al. reference discloses a system in which an array is used as a small container. Each reaction or interaction carried out on the array could be equivalently carried out using soluble reagents in a solution in a container (e.g., a tube or microtiter well). The only benefit of the array in such a conventional system is that it is smaller and easier to handle than a microcentrifuge tube or a well of microtiter plate.

For example, the reactions disclosed by the Shair et al. reference for determining enantiomeric excess could equivalently be carried out using soluble reagents in solution. The soluble reagents would yield the same range of detectable colors. Using solution in a tube or well would be less convenient, but the results would be the same. This reference merely uses an array as a small container for interactions and reactions that occur readily with all of the reagents free in solution.

In contrast, the presently claimed methods provide binding interactions that **cannot** be obtained in solution. The presently claimed methods employ a plurality of different building block molecules immobilized in proximity to one another on the support to bind a test ligand. The building block molecules being immobilized in proximity to one another on the support provides the interactions that bind the test ligand. If the building block molecules were free in solution, perhaps one individual building block might have some affinity for the test ligand, but there would be no cooperativity among the plurality of different building block molecules. Thus, the soluble building block molecules could **not** work together to bind to the test ligand with significant affinity, specificity, or sensitivity. Therefore, for yet another reason, the Shair et al. reference neither teaches nor suggests the presently claimed methods.

The secondary references do not remedy the shortcomings of the primary reference. Thus, the combined references fail to render the presently claimed invention obvious.

Conclusion

Accordingly, based on at least the foregoing differences, Applicant respectfully submits that the Shair et al. reference, either alone or in combination with other references, neither teaches nor suggests the presently claimed methods.

Summary

In view of the above remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Please charge any additional fees or credit any overpayment to Merchant & Gould P.C., Deposit Account No. 13-2725.

Respectfully submitted,

MERCHANT & GOULD P.C.
P.O. Box 2903
Minneapolis, Minnesota 55402-0903
(612) 332-5300

Date: 19 Jan '10

Mark T. Skoog
Reg. No. 40,178

MTS:kf